Dendritic cells in pregnancy and pregnancy-associated diseases

Ran Wei[a], Nannan Lai[b], Lin Zhao[a], Zhen Zhang[a], Xiaoxiao Zhu[a], Qiang Guo[a], Chu Chu[a], Xiaoxiao Fu[a], Xia Li[a,*]

[a] Laboratory for Molecular Immunology, Institute of Basic Medicine, Shandong Provincial Hospital Affiliated to Shandong First Medical University, Jinan, Shandong, PR China [b] Scientific Research Center, The Seventh Affiliated Hospital of Sun Yat-sen University, Shenzhen, Guangdong, PR China

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ABSTRACT

Dendritic cells (DCs) play a critical immuno-modulating role in pregnancy, which requires the maternal immune system to tolerate semiallogeneic fetus and at the same time to maintain adequate defense against pathogens. DCs interact closely with other immune components such as T cells, natural killer cells and macrophages, as well as the endocrine system to keep a pregnancy-friendly environment. Aberrant DC activities have been related to various pregnancy-associated diseases such as recurrent spontaneous abortion, preterm birth, pre-eclampsia, peripartum cardiomyopathy and infectious pregnancy complications. These findings make DCs an attractive candidate for prevention or therapy on the pregnancy-associated diseases. Here, we review recent findings that provide new insights into the roles of DCs in pregnancy and the related diseases. We also discuss the medical potentials to manipulate DCs in clinics. Whereas this is an emerging area with much work remaining, we anticipate that a better understanding of the role of DCs in maternal-fetal immunotolerance and a therapeutic manipulation of DCs will help women suffering from the pregnancy-associated diseases.

1. Introduction

Dendritic cells (DCs) of the modern immunological concept were identified in the peripheral lymphoid organs of mouse by Steinman et al. in 1970s [1–3]. The finding that DCs are the potent and principal stimulators of the mixed lymphocyte reaction [4,5], initiated decades of intensive researches on its importance in immunity. Nowadays, DCs are best known for their unique status in the immune system. They are not only a bridge between the innate and adaptive immunity, but also a teeterboard between the immunity response and tolerance. DCs can capture and process pathogens as an innate immune component, and then present antigens as simulating signals to the naïve T cells to trigger adaptive immune response [6]. Furthermore, DCs can induce both the central and peripheral tolerance via extending the maintenance of immune homeostasis and blocking autoimmune responses [7].

Gradually, studies on the immuno-regulation abilities of DCs expanded to the reproductive immunology at the turn of the century [8, 9]. Accumulating studies demonstrated that the features and functions of DCs in uterus (particularly in human decidua) as well as of DCs in peripheral blood (PB), change in line with the pregnancy process [10–12]. These findings demonstrated that DCs play an essential role in the fetal immune tolerance and in other maternal physiological adaptions after the fertilization, such as decidualization and angiogenesis [13–16]. Indeed, DCs have been found to interact with other immune cells, eg. T cells, natural killer cells (NK cells) and macrophages, as well as respond to the dramatic hormone fluctuations during pregnancy [17–20]. The aberrant differentiation and/or functions of DCs are involved in various pregnancy-associated diseases, such as recurrent spontaneous abortion (RSA), preterm birth (PTB), preeclampsia (PE), peripartum cardiomyopathy (PPCM) and infectious pregnancy complications [21–25].

In this review, we will summarize the current concepts concerning the roles of DCs in pregnancy, their characteristics in pregnancy- associated diseases, and their clinical potentials.

2. DC subgroups in pregnancy

The progress on the studies of DCs in the reproductive immunology is relatively tardy. One reason is that there are no exclusive surface markers for human DCs to distinguish them from other immune cells [26]. Human DCs are usually identified as human leukocyte antigen (HLA)-DR$^+$ cells, with absence of lineage-specific markers (lin) for T cells (CD3), B cells (CD19), macrophages (CD14), and NK cells (CD56/CD16) [27]. In comparison, the markers for murine DCs are relatively explicit, as major histocompatibility complex (MHC)-II$^+$ CD11c$^+$ [28]. Another obstacle is that DCs are highly heterogeneous and can be divided in into subgroups with disparate phenotype, morphology and function. The classification standards of DC subgroups could be their lineage position, development status, tissue distribution, immune function, or the expression of surface molecules [29,30]. The third reason to impede the DC studies is that there are no consistent markers for human and rodent DC subgroups, though they are comparable in their development and functions [31,32]. Despite of all

* Corresponding author at: Laboratory for Molecular Immunology, Institute of Basic Medicine, Shandong Provincial Hospital Affiliated to Shandong First Medical University, 18877 Jingshi Road, Jinan, 250062, Shandong, PR China. *E-mail address:* lixia@sdfmu.edu.cn (X. Li).

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these obstructions, some consensus opinions for the role of DCs in pregnancy can still be summarized from the diverse, inconsistent and sometimes even incompatible studies. The characteristics of DCs change dynamically during pregnancy, in a tissue-specified manner [33,34]. Compared to the total DC level, the composition and functions of DC subgroups are crucial for the delicate balance of the maternal-fetal immune tolerance [35,36].

In this part, the general features and functions of the DC subgroups are introduced, along with their performances in pregnancy and pregnant-associated diseases. Data from both human and mice were included.

2.1. cDCs, pDCs, mono-DCs and LCs

Based on their lineage position, DCs can be divided into four subsets: the conventional DCs (cDCs, also called myeloid DCs), the plasmacytoid DCs (pDCs, also called lymphoid DCs), the monocyte-derived DCs (mono-DCs) and the Langerhans cells (LCs). In the classical DC development model (Fig. 1), the derivation of DCs in the bone marrow follows a lineage of the hematopoietic stem cells (HSCs) to the common myeloid progenitors (CMPs), then to the monocyte and dendritic cell progenitors (MDPs) [30]. MDPs differentiate into the common monocyte progenitors (CMOPs) and the common DC progenitors (CDPs). The latter develop further into two main subsets of DCs, cDCs and pDCs [30]. cDCs are the original DC type that Stainman et al. discovered, and account for the major proportion of DCs. Their main functions are to capture, process and present antigens to T cells, either inducing specific immune responses against invading pathogens or enforcing self-tolerance [37]. The minor portion of DCs, pDCs, express low levels of MHC-II and costimulatory molecules, and secrete paramount amounts of interferon (IFN)-α in response to viral infections [38,39]. Mono-DCs, as their name implies, derive from monocytes in blood under some inflammatory conditions *in vivo*, and are relatively scare in homeostasis [40,41]. LCs have a unique embryonic origin compared to the other three subsets. They may either derived from fetal liver monocytes or yolk sac-derived macrophages [42]. Then, LCs remain in the epidermis and mucosa as resident sentinels that could capture antigen, migrate to lymph nodes and develop potent immune-stimulatory capacity [42,43]. The whole derivation process of DC subsets is under the control of cytokines, transcription factors and other epigenetic regulations [44–46].

While all the four DC subsets are found in the female reproductive tract, the studies on immune changes in pregnancy are mainly focused on cDCs and pDCs (Table 1). cDCs and pDCs were found presenting in PB and decidua throughout the pregnancy [47,48]. In pregnant women, the decidua had more cDCs but less pDCs than PB [48] The increase secretions of the human chorionic gonadotropin (HCG) helps keeping the delicate balance of cDC and pDC, although it is may not be a key regulator of the cellular alterations [49]. However, the changes of cDCs and pDCs described in different studies are diverse, as different surface markers, maternal samples, and gestation stages were chosen. Nonetheless, the results of most studies showed that the ratio of cDC/pDC in pregnant women was higher than in non-pregnant women, despite the frequency of cDCs and pDCs were reported to be higher, lower or

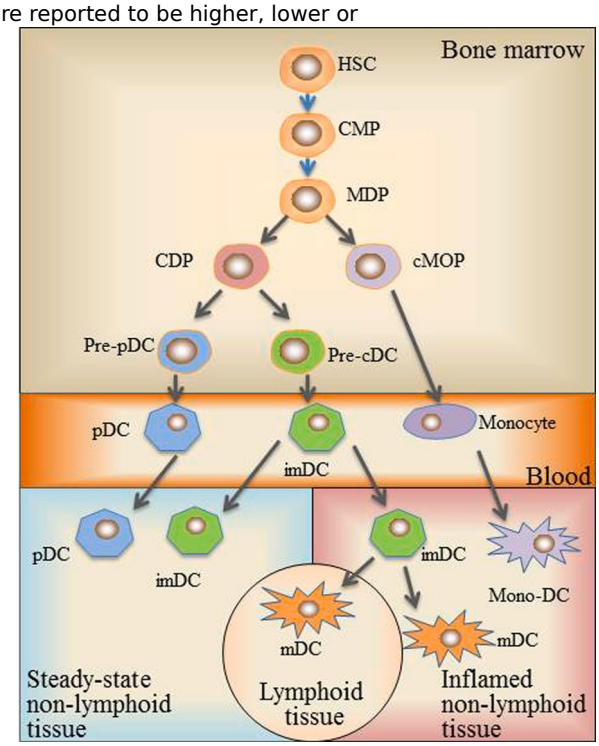

Fig. 1. The classical development model of DCs.
In the classical DC development model, the hematopoietic stem cells (HSCs) in the bone marrow derive to the common myeloid progenitors (CMPs), and then to the monocyte and dendritic cell progenitors (MDPs). MDPs differentiate into the common monocyte progenitors (CMOPs) and the common DC progenitors (CDPs). CDPs develop further into two types of DC progenitors for the conventional DCs (Pre-cDCs) and plasmacytoid DCs (Pre-pDCs). Pre-cDCs migrate from the bone marrow into blood and non-lymphoid tissues, keeping an immature status (imDCs) in the steady state. imDCs mature into mDCs when they contact with the pathogens and migrate into the lymphoid tissues, such as lymph nodes. Monocyte-derived DCs (mono-DCs) also present in the inflamed non-lymphoid tissues.

constant respectively [47,50,51]. The increase of cDCs, with or without the decrease pDCs, seems to account for the higher ratio [11,47,51]. Interestingly, in mouse, the ratio of cDC/pDC was reported to decrease in pregnancy compared to the non-pregnant controls [34,52]. However, due to the very limited number of studies addressed the proportion issue of cDCs and pDCs, more thorough and systematic tests should be made on this issue in human and mouse before any conclusions are made. Besides of the proportion changes, the expression of the surface molecules on cDCs and pDCs also fluctuate following the pregnancy process, which represents the altered DC functions. For example, Darmochwal-Kolarz et al. found that the expression of CD200, CD200R, B7-H1 and B7-H4 on both cDCs and pDCs were higher in the first trimester than that in the luteal phase of ovarian cycle [53,54]. As the pregnancy proceeds, CD200 and B7-H1 on cDCs researched their peak level at the second trimester, and then decreased in the third trimester [53,54]. The changes of cDCs are accompanied by reduced antigen-specific T cell responses and the increased regulatory T (Treg) cells numbers [17,51]. The

mechanism underlying these phenomenon need to be further investigated.

Studies on mono-DCs and LCs in pregnancy are much less than cDCs and pDCs. A preliminary study showed that in the first trimester, mono- DCs accumulated in decidua while negligibly exist in PB [55]. Compared to the non pregnant women, mono-DCs derived from PB of pregnant women expressed less CD80, CD86 and HLA-DR molecules, and secreted more interleukin (IL)-10 in response to the inflammatory stimuli [33]. The connection between LCs and pregnancy has been ignored, even though they have been found to exist in the female productive tract long

Table 1
Changes of cDCs and pDCs in pregnancy

Year	Authors	Species	Samples	Groups	Pregnancy phages	cDC markers	pDC markers	Results
2003	Darmochwal-Kolarz et al. [47]	Human	PB	NP vs. NC	GT 1, 2, 3			
2003	Gardner et al. [11]	Human	Decidua	NP				
2003	Miyazaki et al. [48]	Human	PB Decidua	NP				
2003	Yoshimura	Human	PB	NP et al. [35]				
2003	Ueda et al. [161]	Human	PB	NP vs. NC				
2004	Blois et al. [68]	Mouse	PB Uterus	NP vs. NC				
2007	Zarnani et al. [34]	Mouse	Uterus Spleen	NP vs. NC				
2008	Bachy et al. [33]	Human	PB	NP vs. NC				
2009	Shin et al. [50]	Human	PB	NP vs.				NC
2011	Della Bella	Human	PB	NP vs. et al. [162]				NC
2011	Escribese et al. [163]	Human	PB	NP				
2012	Cordeau et al. [164]	Human	PB	NP vs. NC		CD1c$^+$ CD19–	BDCA-2$^+$ CD123$^+$	

-12	lin– HLA-DR$^+$ CD1c$^+$	lin– HLA-DR$^+$ D123$^+$	
9 ± 1.3 -32	lin–HLA-DR$_{bright}$ CD11c$_+$ lin–CDw123–CD11c$^+$HLA-DR$^+$	lin– HLA-DR$_{bright}$CD123$_+$	
		lin–CDw123$^+$ CD11c–HLA-DR$^+$	
)– 35	lin–HLA-DR$^+$CD123–CD11c$^+$	lin–HLA-DR$_+$CD123$_{bright}$	
.5, 3.5, .5, 7.5, 10.5, 15.5, or	CD11c$^+$ CD8a–	CD11c$^+$ CD8a$^+$	
11, or 18	CD11c$^+$ CD11b$^+$	CD11c$^+$ CD8a$^+$	
)– 41	lin–HLA-DR$^+$ CD11c$^+$	lin–HLA-DR$^+$CD11c–	
very	CD11c$^+$	CD11c– CD123 ^{bright}	
2, 3	lin–HLA-DR$^+$CD11c$^+$	HLA-DR$^+$ lin–CD123$^+$	
– 20	CD1c $^+$	CD303$^+$	
	NA	HLA-DR$^+$ lin–BDCA4$^+$	

cDCs and pDCs were present throughout the pregnancy. In pregnant women, GT 2 exhibited the lowest percentage of cDCs and pDCs, but the highest cDC/pDC ratio compared to GD 1 and 3. cDCs were identified, comprising 1.7 % of the decidual leukocytos.

They were DC-SIGN– while DC- SIGN$^+$ are generally expected in DCs. No LCs and pDCs were detected. Two subsets of cDCs were distinguished on the high or modified expression of HLA-DR and DC-activation markers. The percentage of cDCs in the decidua was higher than that in PB, whereas pDCs was lower. cDCs in the decidua secreted less IL-12 than that in PB, and induced a higher percentage of Th2 cells. The frequency of cDCs increased in the late stage of pregnancy, while that of pDCs gradually decreased. HCG induced the maturation of both DC subsets in conjunction with increases in the cytokine secretion such as IL-12 and IFN-γ. Compared to the controls, the percentages of cDCs and pDCs were lower in the PB obtained from pregnant women at delivery, whereas the ratio of cDC/pDC

Year	Authors	Species	Samples	Groups	Pregnancy phages	cDC markers	pDC markers	Results
								was not reduced. The vast majority of uterine DCs were mDCs. There were two peak of pDCs present on GD 1.5 and 5.5. When compared with other stages of pregnancy or non-pregnant mice, uterine pDCs was higher, while cDCs and cDC/pDC ratio were lower at mid-gestation. Meanwhile, splenic cDCs decreased and pDCs did not change. The circulating cDCs expressed less CD86 and HLA-DR in the third trimester compared with non- pregnant women, indicating that they are modified to favor Th2 responses. The ratio of cDC/pDC in pregnant women was higher than that in the controls. HLA-DR expressions on cDCs in pregnant women were less than that in the controls. Both cDCs and pDCs undergo a state of incomplete activation, which are more evident in GT 3. Glycoprotein hormone activin-A may contribute to DC incomplete activation. DEFA 1–3 was produced constitutively from cDCs and pDCs3, but the production from cDCs was reduced in the later stages of pregnancy. E_2 inhibited DEFA 1–3 production from cDCs but not pDCs. PG does not affect DEFA 1–3 in any of the DC populations. pDCs frequency and the co- stimulatory receptors CD54 and CD86 on pDCs were decreased from (*continued on next page*)
Year	Authors	Species	Samples	Groups	Pregnancy phages	cDC markers	pDC markers	Results
								pregnant women as compared to controls.
2012	Darmochwal-Kolarz et al. [53]	Human	PB	NP vs. NC	GT 1, 2, 3	$CD1c^+$ CD19–	BDCA-2^+	cDCs and pDCs showed an increased tolerogenic properties in GT 1, as the expression of CD200 and CD200 receptors increased when compared to the controls.
2015	Kwiatek et al. [129]	Human	PB	NP vs. NC	GW 6− 13	BDCA-1^+ CD19–	BDCA-2^+ $CD123^+$	Older maternal age and obesity reduced the percentage of circulating cDCs and pDCs.
2016	Fang et al. [104]	Mouse	Decidua Spleen LN	NP	GD 8.5 and 13.5	$CD11c^+$	CD11c–	The differentiation of cDCs and pDCs is regulated in a tissue-specific manner during pregnancy. The cDC/pDC ratio remained constant in the spleen, but reduced in the para-aortic LNs because of the decrease of cDCs and increase of pDCs. In the para-aortic LNs, the expansion of Treg cells were positively correlated with that of pDCs, but negatively correlated with cDCs. In decidua, there was no
2017	Shah et al. [17]	Human	PB	NP vs. NC	GT 2, 3	Lin–HLA-DR^{high} CD14–CD123–	Lin–HLA-DR^+CD14–$CD123^+$	such correlations. Reduced antigen-specific T cell responses associated with reduced proportions of cDCs in the mid gestation.
2018	Li et al. [52]	Mouse	Decidua Placenta	NP vs. NC	GD 6, 7, 8, 12, 13, 14, 16, 17, 18	lin– $CD11c^+$ IA/I-E^+ B220–$CD11b^+$ CD8a–	lin– $CD11c^+$ IA/I-E^+ B220– CD11b– $CD8a^{\pm}$	Both frequency and composition of decidual DCs changed across gestation. cDCs and pDCs exhibited a V type and an opposite V type fluctuation respectively.
2019	Ehrentraut et al. [51]	Human	PB Placenta	NP	GT 1, 2, 3	$CD1c^+$ OR $CD141^+$	$CD303^+$	cDCs increased during the first and second trimester, while pDCs were not altered during normal pregnancy.

Table 1 (*continued*)

cDCs: conventional dendritic cells; pDCs: plasmacytoid dendritic cells; PB: peripheral blood; LN: Lymph node; NP: normal pregnancy; NC: non-pregnant control; GT: gestational trimester; GW: gestational week; GD: gestational day; LCs: langerhans cells; DC-SIGN: dendritic cell-specific HIV-1-binding protein; HCG: human chorionic gonadotropin; IL: interleukin; IFN: interferon; PG: progesterone; DEFA: α-defensin; E_2: estrogen.
NA: not available.

since [56,57]. It is probably because they are more like to defense against antigens and trigger immune responses than to induce immune tolerance [58]. Therefore, the role of mono-DCs and LCs in pregnancy requires more in-depth research.

2.2. imDCs and mDCs

Based on their maturity, DCs can be divided into immature DCs (imDCs) and mature DCs (mDCs). These two subgroups were originally identified under the setting of cDCs, as populations in two distinct maturational stages (Fig. 1) [59,60]. In this background, imDCs are continuously produced from HSC within the bone marrow and migrate through the blood into other tissues, where they stay as “surveillance polices”, inducing immune tolerance rather than immune response [61]. When being stimulated by antigens, imDCs develop into mDCs,

expressing MHC-II and T-cell costimulatory molecules such as CD80, CD86,and CD40 on high levels [62]. Then, mDCs migrate to the secondary lymphoid organs and stimulate naïve T cells proliferation and differentiation, inducing immune responses against pathogens invasion [60] In addition to their maturation process from imDCs, mDCs can be differentiated directly from monocytes both *in vivo* and *in intro* [63,64]. Both imDCs and mDCs have been found in human decidua [9,11]. Particularly, a unique type of DC-SIGN^{+} (CD209^{+}) DCs that had characteristics of imDCs was found in decidua, but not in endometria [65]. Compared to non-pregnant women, the predominance of imDCs in decidua of the pregnant women were more obvious, because of the rapid increase of imDCs and the constant of mDCs level [66,67]. The predominance of imDCs in uterus is also existed in pregnant mice, although the changes of imDCs and mDCs are different from human [68]. In mice, imDCs in uterus exhibited an upward-downward-upward fluctuation pattern while mDCs exhibited a downward-upward-downward pattern [68,69]. Table 2 listed the findings concerning imDCs and mDCs in human and mice.

The study of Kwan et al. divided decidual DCs of human in more detail as three groups, imDCs, mDCs and intermediate DCs, and found intermediate DC declined in the second trimester that the first trimester. Their finding indicated that the reason for the increasing imDCs level in pregnancy may, at least partly, due to the development process from imDCs to mDCs was blocked [70]. The predominance of imDCs may represent the altered functions of DCs in pregnancy. mDCs in decidua produce less IFN-γ, tumor necrosis factor (TNF)-α and IL-15 cytokines in their cytoplasm and cause weaker proliferation of NK cells in contrast to imDCs [33]. Meanwhile, mDCs in decidua have less ability to produce IL-12 and induced the differentiation of Th2 responses compared to PB mDCs [48]. All of these findings indicated that the immune-stimulating abilities of DCs were reduced in decidua.

In another aspect, mDCs derived from monocytes are also present in human decidua at the 1 st trimester of pregnancy in higher number, while they were in negligible concentration in PB in pregnant women [55]. *in vitro*, DCs derived from monocytes from pregnant women was "less mature" than that of non-pregnant women, revealing by their lower levels of CD80, CD86 and HLA-DR, and less IL-12 secretion but more IL-10 secretion in response to inflammatory stimuli [33].

Putting together, it seemed that the immature status of DCs is benefit

Table 2
Changes of imDCs and mDCs in pregnancy.

Year	Authers	Species	Samples	Groups	Pregnancy phages	Markers for imDCs	Markers for mDCs	Results
2000	Kammerer et al. [9]	Human	Decidua	NP	GW 6− 9	NA	$CD45^+$ $CD40^+$ HLA-DR^+ $CD83^+$	mDCs were found in human early pregnancy decidua.
2003	Kammerer ¨ et al. [65]	Human	Decidua	NP vs. NC	GW 7− 8 and at term	HLA-DR^+ $CD14^+$ DC-$SIGN^+$	$CD25^+$ $CD83^+$	DC-SIGN + cells were first identified in decidua, but not in endometria. They showed functional features of imDCs, and efficiently matured into mDCs *in vitro*.
2003	Miyazaki et al. [48]	Human	PB Decidua	NP	GT 1	NA	$CD83^+$	Decidual DCs express mature, costimulatory markers such as CD83, CD80 and CD86. However, they had less ability to produce IL-12 and induced the differentiation of Th2 responses compared to DCs in PB.
2003	Gardner et al. [11]	Human	Decidua	NP	GW 7–12	$D86_{low}$ $CD40_{low}$ $CD205^{low}$	NA	The decidual DCs had the phenotype of imDCs.
2003	Blois et al. [68]	mouse	PB Uterus	NP vs. NC	GD 1.5, 3.5, 5.5, 6.5, 7.5, 8.5, 10.5, 13.5, 15.5, or 17.5	MHC II–	MHC II^+	mDCs in dicidua at the early and late pregnancy were similar to uterus of non-pregnant mice, while they diminished in the middle pregnancy.
2005	Ivanova et al. [55]	Human	Decidua	NP	GW 8–12	NA	HLA-DR^+ $CD83^+$	mDCs are present in human decidua in higher number, while in mDC in PB were found in negligible concentration.
2007	Aldebert et al. [66]	Human	PB Plancental blood	NP vs. NC	At delivery	CD83–	$CD83^+$	Compared to non-pregnant women, imDCs in pregnant women increased, while mDCs was at the identical level.
2008	Laskarin et al. [111]	Human	Decidua	NP	GW 6–10	$CD1a^+$	$CD83^+$	mDCs produce less IFN-γ, TNF-α and IL-15 cytokines in their cytoplasm and cause weaker proliferation of NK cells in contrast to imDCs.
2014	Bartmann et al. [67]	Human	Decidua	NP	GW 6− 40	DC-$SIGN^+$	$CD83^+$	imDCs increased until term.
2014	Kwan et al. [70]	Human	Decidua	NP	GW 6− 12 and GW 13− 20	DC-$SIGN^+$	$CD83^+$	Maturation of DC precursors to inflammatory mDCs is inhibited within the decidua, as no change in imDCs and mDCs were observed, yet a significant decline in intermediate $CD205^+$ DC.
2015	Chernykh et al. [71]	Human	PB	NP vs. NC		$CD86^{low}$ $CD80^{low}$	$CD83^+$	DCs induced from blood monocytes from pregnant women had a reduced number of $CD83^+$ and $CD25^+$DCs, and less ability to stimulate Th2 cells responses and to induce T cell apoptosis, compared to those from non-pregnant women.
2019	Gu et al. [69]	Mouse	Uterus.	NP	GD 7	$CD86_{low}$	$CD86_{high}$	More than 70 % were imDCs, whereas mDCs accounted for less than 30 % of the total uterine DCs. imDCs exhibited an upward-downward-upward fluctuation pattern during the early pregnancy, while the pattern of mDCs was on the contrary.

imDCs: immature dendritic cells; mDCs: mature dendritic cells; PB: peripheral blood; NP: normal pregnancy; NC: non-pregnant control; GW: gestational week; GD: gestational day; IL: interleukin; IFN: interferon; TNF: tumor necrosis factor; Th2: helper T cells type 2.
NA: not available.

for the maternal-fetal tolerance. However, the regulating mechanism still not fully clarified. Recently, some preliminary studies showed that dehydroepiandrosterone and cytochrome P450 26A1 may play a role in modulates decidual DCs [69,71].

2.3. Circulatory DCs, migratory DCs and resident DCs

Based on their distribution, DCs can be classified into circulatory DCs in PB, migratory DCs in the non-lymphoid tissues and resident DCs that spend their entire lives within the lymphoid tissues [30,72]. While circulatory DCs is a complexity of almost all kinds of DCs, migratory DCs and resident DCs have their distinct functions. Migratory DCs can be activated by antigens, and then migrate to the tissue-draining lymph nodes through the lymphatics, presenting antigens to T cells [73]. Resident DCs in the central lymphoid organ are involved in the negative selection of T cells; whereas in the secondary lymphoid organs, resident DCs perform the antigen presentation function to $CD4^+$ T cells [74,75].

Studies on DCs in pregnancy usually use blood samples as they are easier to be collected and uterus samples (particularly decidua or placenta samples in human) as they represent the immune environment on the maternal-fetal interface more precisely. It should be noticed that quantitative, functional and subset composition differences of DCs in blood and uterus were not exactly the same [17,51,66].

In the other aspect, differences of resident DCs during pregnancy got less attention compared to the circulating DCs and migratory DCs, although the lymphoid organs are also important as the “hidden” maternal-fetal interface [76]. In mice, decidualization inhibited emigration of DCs in decidua to the neighboring draining LNs, and subsequently,

minimized the exposure of T cells in LNs to fetal/placental antigens [10]. A preliminary study found that reduced cDCs number and increased pDCs number in the para-aortic LNs in pregnant mice, while they remained constant in spleen, which indicated that resident DCs regulated the immune system in a tissue specific manner in pregnancy [77]. Meanwhile, percentages of Treg cells to the leukocytes increased in the para-aortic LNs, consistent with the increase of pDCs and inversely correlated with cDCs [77]. It accorded with the studies in allograft tolerance that pDCs mediated tolerance in the secondary lymphoid organs [78].

2.4. Tolerogenic DCs and inflammatory DCs

Based on their main functions, DCs can be divided into two subsets as tolerogenic DCs (also called regulatory DCs) and inflammatory DCs. The former constantly exist in the tissues, regulating immunity, or in other words, restricting immune reactions to induce specific tolerance [79–81]. The latter is thought to exist transiently only during the inflammation, secreting inflammatory cytokines to promote immunity response that leads to the clearance of pathogens or tumors [82,83].

It is supposed that tolerogenic DCs should be in a dominate position in most time of pregnancy, to maintain the maternal-fetal tolerance. It is found that progesterone (PG), HCG, tumor-associated glycoprotein (TAG) and macrophage inhibitory cytokine-1 (MIC-1) existed in the maternal environment, helped keeping DCs in a tolerogenic state [49, 84–86]. For example, PG suppressed the ability of DCs to produce the pro-inflammatory response-promoting cytokines TNF-α and IL-1β *in vitro*, but not the anti-inflammatory cytokine IL-10 [84]. Besides of the maternal factors, fetal components, such as amniotic mesenchymal tissue cells and chorionic villous mesenchymal stem cells, also help enhance the function of tolerogenic DCs [87,88]. For example, the amniotic mesenchymal tissue cells abolished the production of inflammatory cytokines such as TNF-α, C-X-C Motif Chemokine Ligand(CXCL) 10, CXCL9, and C-C Motif Chemokine Ligand 5 (CCL5) *in vitro* [87].

Inflammatory DCs also exist in normal pregnancy without any infections or pathological inflammations, and play important roles during the embryo implantation and parturition, [17,89,90] while the most part of pregnancy requires a tolerant environment [91–93]. Unlike the former opinion that pregnancy requires the restricted immune functions, the modern theory is that pregnancy is a dynamic and well-regulated immune process [94], which requires the collaboration of both tolerogenic and inflammatory DCs.

3. Functions of DCs in pregnancy

Despite of their minute proportion in the leukocytes in decidua, DCs have a unique regulatory ability in the subtly balance of the immune response and tolerance, by interacting intimately with T cells, NK cells and macrophages (Fig. 2) [95,96]. Meanwhile, DCs are subject to various microenvironmental factors, including the pregnancy-related hormones whose levels are dramatically changed during pregnancy. In the sophisticated maternal-fetal immune network, DCs is an elegant arbiter [94].

3.1. Interaction between DCs and T cells in pregnancy

As the most potent antigen-presenting cells (APCs) in the immune system, DCs have the crucial ability to initiate the differentiation of naïve T cells into several subsets, eg. helper T cells type 1 (Th1), type 2 (Th2), type 17 (Th17) and Treg [97]. So, when Saito et al. explained the maternal-fetal tolerance using the change of immune active Th1/Th17 predominance to immune tolerant Th2/Treg predominance, they actually highlighted the role of DCs that behind T cells [98]. Simply speaking, cDCs and pDCs promote Th1 and Th2 immunities respectively, regulating TH1/TH2 balance in human pregnancy [99]. In mouse, Negishi Y et al. attributed the Th1/Th2 balance to two more specific DC subsets in mouse, that DEC-205$^+$ DCs having the capacity to establish Th1 polarization while 33D1$^+$ DCs to induce Th2 dominance [36]. The DEC-205$^+$/33D1$^+$ ratio decreased gradually with the progress of pregnancy, but rapid increased around delivery *in vivo* [100]. This change of DCs represented Th1 was reduced in pregnancy unless they are needed by the delivery, and they are coincident with human in the aspect that Th1 were decreased in pregnancy. However, the relationship between DCs and T cells may not be that simple and exclusive. For example, cDCs in human decidua were found to secret less IL-12 and induced a higher percentage of Th2 in comparison with the peripheral cDCs [48]. It demonstrated that cDCs could induce Th1 or Th2 response according to their environment. In mice, cDCs induce a vigorous proliferative response in CD4$^+$ T cells, whereas pDCs induce a limited CD4$^+$ T cell response that is associated with marked T-cell apoptosis [101]. It enlightened that more interactions of DCs and T cells should be considered, rather than only discussion of the DC secretion of Th1 or Th2 cytokines.

Decidual DCs also induced proliferation and differentiation of T cells into Treg cells through the transforming growth factor β (TGF-β) [102]. These induced Treg cells display immunosuppressive functions by expressing Th2-type cytokines, promoting invasiveness and HLA-G expression of trophoblasts, and reducing cytotoxicity in CD56^{bright} CD16$^-$ NK cells [102]. DC regulation on Treg cells may related to the secretion of IL-10, which is essential in inducing adaptive regulatory T cells [103]. Keeping the immature status of DCs and the balance of cDCs and pDCs also contribute to the expansion of the Treg population [104, 105].

Besides their impacts on these CD4$^+\alpha\beta^+$ T cells, DCs have the ability to up-regulate $\gamma\delta^+$ T cells that were showed to suppress the immune system during pregnancy by some earlier studies [106,107]. This effect should not be overlooked.

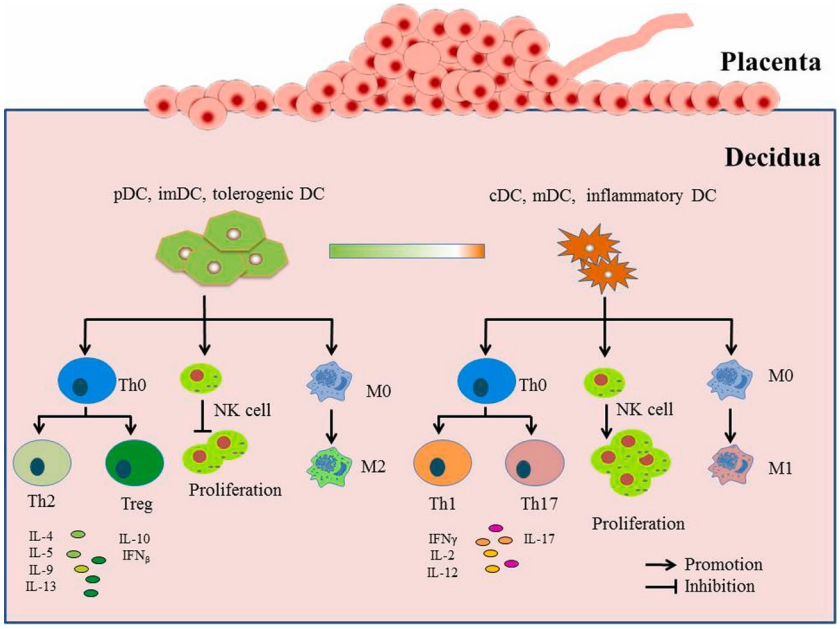

Fig. 2. The regulatory functions of DCs in pregnancy. Immune cells in decidua include DCs, T cells, NK cells and macrophages. DCs interact with other immune cells to maintain the maternal-fetal immunotolerance. In decidual, imDCs or tolerogenic DCs are in precedence compared to mDCs or inflammatory DCs. The regulation abilities of DCs includes adjusting the differentiation of T cell subsets, inhibiting the proliferation of NK cells, and possibly affect macrophage polarization.

3.2. Crosstalk between DCs and NK cells in pregnancy

Induction of the innate response through DC-mediated NK cells activation, and adaptive immune response through NK-mediate DC editing and maturation has been elucidated In recent years [108]. The liaison of NK cells and DCs in the decidualization and angiogenesis has caused attention long since, and reviewed by several excellent articles [15,18,109]. Moreover, the reciprocal cross-talk between DCs and NK cells in decidua maintains across the pregnancy, in a direct way by cell-to-cell contact or in an indirect way by cytokine secretion. Kammerer et al. found that in human decidua, over 60 % imDCs were in ¨ close proximity with NK cells [65]. This cluster phenomenon was only found in the maternal-fetal interface, but not in the endometrium of non-pregnancy, suggesting a pregnancy-specific interaction of DCs and NK cells [110]. It was demonstrated that only one-third of $CD56^{+}$ NK proliferated when co-cultured with imDCs, indicating a selective expansion of NK controlled by imDCs [111]. In the other direction, imDCs presented an apoptosis-like morphology in the presence of DC-NK conjugation in the cell suspensions isolated from human decidua, indicating NK also affect DC proportion [110]. As for the cytokines-involved indirect interaction between DCs and NK cells, Karsten et al. found that the implantation sites lacking DCs are characterized by decreased IL-15 and IL-12 mRNA and/or protein levels, causing the decreased frequency, reduced size and lower IFN-γ expression of NK cells [112]. In summary, the direct and indirect intimate cross-talk between DCs and NK cells are beneficial for pregnancy outcome.

3.3. Relationship of DCs and macrophages in pregnancy

DCs and macrophages share the same monocytes origins and some phenotypical and functional characteristics [113]. As B cells are fairly absent in decidua, macrophages and DCs are the main APCs at the maternal-fetal interface, and have similar immune control abilities in a complementary way [114]. In the first trimester, IL-1β and TNF-α induce macrophages- and DC-recruiting chemokine production through the NFκB and MAPK pathways, triggering the accumulation of DCs and macrophages in decidua [115]. Among these chemokines, CCL2 is the main chemoattractant for macrophages, and CCL5 is the main chemoattractant for imDCs [115]. Macrophage growth factor colony-stimulating factor (M-CSF) also affects the recruitment of macrophages and DCs into decidua in a CCR2-independent way [19]. Interestingly, decidual macrophages were found to be differentiated into DC-like cells with immunosuppressive properties in the second trimester of pregnancy, but into DC-like cells with immunostimulatory properties in the third trimester of pregnancy, exhibiting a maternal-fetal immunotolerance to maternal-fetal immunorejection [116]. These two types of macrophages may represent the inflammatory classically activated macrophages (M2) and tolerogenic alternatively activated macrophages (M1) subsets [117]. it implies that DCs may have the ability to adjust the macrophage polarization in pregnancy. *3.4. DCs are regulated by hormones in pregnancy*

A balanced and tightly controlled immune-endocrine crosstalk is indispensable for a successful pregnancy. PG and E_2 secreted by placenta, and HCG secreted by chorionic trophoblast cells have been reported to participate in DC differentiation, maturation and function regulation in maternal-fetal interface. When co-cultured with PG, DCs decreased the expression of co-stimulatory molecules and increased production of Th2-skewing cytokines IL-10, which suggested that PG restricts DCs to an immature state for immunotolerance during pregnancy [118,119]. Studies *in vitro* demonstrated that PG inhibits DC maturation by suppressing CD83 expression and inflammatory cytokines production such as TNF-α and IL-1β [55,84]. PG can also block the antigen-presenting ability of DCs and thereby reducing maternal immune activity to maintain maternal-fetal immunotolerance [120]. High level of E_2 in maternal-fetal interface inhibits DCs by secreting pro-inflammatory cytokines such as TNF-α, IL-1β, IFN-γ and IL-12. [121] In addition, E_2-mediated ERα signaling may decrease the numbers of CMPs and thereby reducing CMPs-derived DCs, which may regulate the immune function in pregnancy. [122] HCG influences DC proliferation and differentiation

and retains DCs in an immature or tolerogenic state, thereby promoting Tregs increment and supporting fetal survival [123, 124]. So when discussing the dynamic changes of DCs in pregnancy, the dramatically fluctuation of maternal hormones are an important regulating factor.

4. Dcs in pregnancy-associated diseases

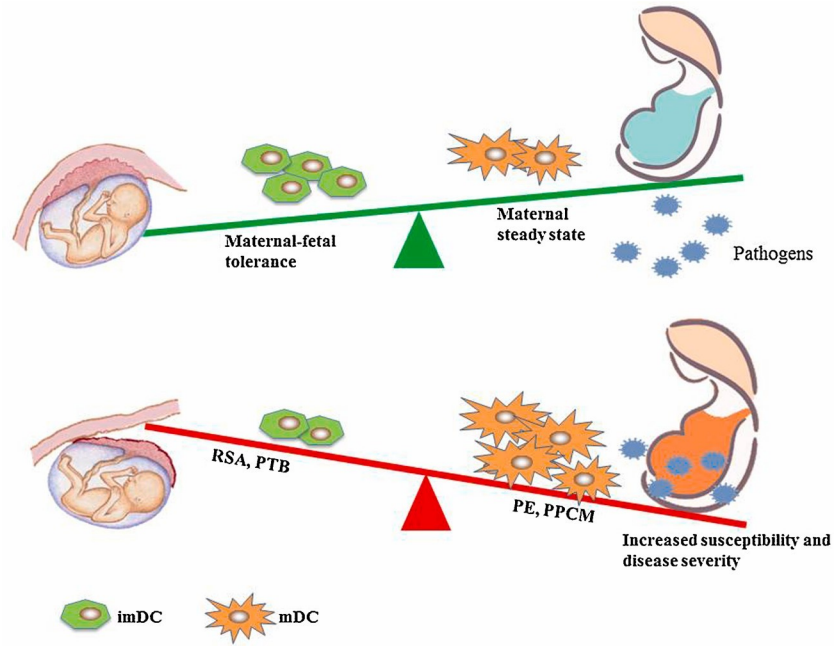

Fig. 3. Abnormal regulatory functions of DCs are harmful to pregnancy.
DCs play a central role in balancing the maternal immune system to tolerate semiallogeneic fetus and at the same time to maintain adequate defense against pathogens. Abnormal functions of DCs could cause immune attack to fetus as in RSA and PTB, and/or to the maternal systems as in PE and PPCM. The immune responses to pathogens could also be lower or higher than usual, inducing an increased susceptibility or an enhanced severity in infection.

The aberrant differentiation and functions of DCs may interrupt the maternal-fetal tolerance, causing fetal rejection as RSA and PTB. Mutually, the interruption of maternal-fetal tolerance may attack the maternal side, eg. the cardiovascular system, causing PE or PPCM. Other than their effects on the tolerance, the abnormalities of DCs may induce the incorrect up- or down-regulation of the immune response, causing infection-related pregnancy complications. In this part, the association of DCs and pregnancy-associated diseases is discussed (Fig. 3).

4.1. DCs in RSA

RSA is defined as two or more consecutive pregnancy losses of clinically recognized pregnancies [125]. Although about 50 % of cases had known causes including abnormal chromosomes, endocrinological disorders and uterine abnormalities, the aetiology of the other half cases is still unknown [126]. Immunological mechanisms are supposed to be involved in these unexplained RSA. Askelund et al. first reported that mDCs in decidua from women with RSA at 8 weeks' gestation are more than the gestational age-matched normal controls, suggesting that DCs were involved in the aetiology of RSA [127]. Qian et al. further discovered not only the increase of mDCs, but also the decrease of imDCs in RSA [128]. These findings were accorded with that the immature status of DCs was benefit to pregnancy, and demonstrated that the inopportune maturation of DCs may play an important role in the pathogenesis of RSA. In the consideration of cDCs and pDCs, Kwiatek et al. found both subgroups in preeclampsia showed no significant difference between RSA and control group, while Huang et al. reported an association between RSA and the elevated level of cDCs in PB [12,129]. Some studies made efforts to find the mechanisms that cause the DC aberrances in RSA, and maternal hormones were brought to the consideration. Results from the studies on spontaneous abortion revealed that PG showed more effects on abortion, compared to E_2 and HCG. [36,51] Laskarin et al. hypothesized that PG reduced the ability of cDCs to induce NK cells proliferation and to secret IL-15, and thus caused abortion in human [130]. However, Schumacher et al. found that PG application did not inhibit the abortion rate in the DBA/2 J-mated CBA/J abortion-prone mice [131]. So, PG and its effect on DCs may not sufficient to explain fetal rejections in RSA. Other mechanisms should be considered, including the roles of DCs in decidualization and angiogenesis during embryo implantation, which is not discussed in this article.

4.2. DCs in PTB

PTB refers to giving birth to babies before gestation week 37 [[132]] It could be regarded as an incorrect-timing parturition, in which the maternal-fetal immune tolerance turns to a repulsive inflammatory status earlier. The inflammation involved in PTB could be caused by infections or just physiological [132,133]. In the lipopolysaccharide (LPS)-treated PTB mouse model that mimic infections, uterine DC activation was observed, suggesting the participation of DCs in the induction of labor [134]. The DC activation in the infection-related PTB was assumed to a downstream mechanism of toll-like receptor 4 (TLR4), because that expanded gestation length co-existed with fewer DCs and more Treg cells in the myometrium in TLR4-deficient female mice [135]. Acute chorioamnionitis (ACAM) is another common cause of PTB, as it represents a physiological inflammation status. DCs obtained from ACAM women

preferentially induced the proliferation of invariant natural killer T cells (iNKT cells), a particular NK cell populations [22]. Study *in vitro* also showed that decidual iNKT cells co-cultured with LPS-pulsed DCs showed significantly decreased extracellular and intracellular IFN-γ secretion and surface CD69 expression [136]. These data demonstrated that the interaction of DCs and NK cells was interrupted in PTB.

4.3. DCs in PE

PE, defined as hypertension after 20 weeks gestation and proteinuria, combined with the presentation of maternal multisystem dysfunction or fetal growth restriction [137].It is associated with an exaggerated systemic inflammatory state that involves the imbalanced Th1/Th17 and Th2/Treg and the resultant changes in pro- and anti-inflammatory cytokine release [23,138,139]. As an important regulatory factor to the balance of Th1/Th17 and Th2/Treg, DCs are assumed to play a role in the pathogenesis of PE. Decidua from PE patients displays elevated levels of several DC-recruiting chemokines, eg. granulocyte-macrophage colony-stimulating factor, indicating more DCs accumulated in uterus of PE than the controls [140,141]. A higher percentage of cDCs, a higher ratio of mDC/pDC and a lower percentage of pDCs was found in PE patients than normal pregnancy subjects [47,142,143]. Correlation analysis found that these DC changes implicated an increased Th1-type immunity and less percentage of Th17 cells [142]. Higher level of decidua mDCs in PE patients also contributed to the increased Th1-type immunity, indicating that the over-maturation of DCs may be one of the potential pathological factors [144]. Studies *in vitro* verified that DCs derived from mononuclear cells in PB of PE patients showed a stronger ability to induce $CD4^+$ T cells differentiation into Th1/Th17 cells [145]. As results of all these DC changes in PE patients, the production of pro-inflammatory cytokines elevated, stimulating an systemic inflammation and maternal injury [146].

4.4. DCs in PPCM

PPCM is a rare and serious heart disease that typically arises in the peripartum period, marked by a rapid onset of left ventricular dysfunction and heart failure in previously healthy women [147]. One hypothesis about PPCM was that cardiac remodeling during the peripartum period resulted in the release of certain cryptic cardiac antigen [24]. Exposure to these antigens caused the maturation of DCs, initiating subsequent cardiac-specific auto-immune responses which may contribute to further cardiac tissue injury. In a normal pregnancy, the maturation of DCs was inhibited, whereas plasma from PPCM patients showed reduced potential for inducing maturation of DC progenitor *in vitro* [24].

4.5. DCs in infectious pregnancy complications

Pregnancy is considered as a unique immunological paradigm which requires the maternal immune system tolerate the semi-allgenic fetus and target pathogenic factors precisely. Pathogens from outside disturb the maternal immune system, inducing either excessive fetal rejection or the deficient pathogen clearance characterized by increased susceptibility and disease severity. Intensive studies have shown that the parasites infection (eg.*Toxoplasma gondii*) and the virus infections (eg influenza virus) caused adverse pregnancy outcomes, such as abortion, stillbirth, intrauterine growth retardation and congenital malformation [148,149]. However, the mechanisms causing these consequences remain unclear. Liu et al. demonstrated that after decidual DCs infected by *T. gondii* enhanced the IFN-γ production and natural-killer group 2, member D (NKG2D) expression on NK cells, leading to an increased cytotoxicity of dNK cells [150]. The same research group found later that the high expression of an inhibitory receptor uman leukocyte immunoglobulin-like receptor subfamily B, member 4 (LILRB4) on DCs were reduced after the *T. gondii* infection, following by the up-regulation of the functional molecules CD80, CD86, and MHC-II expressions on DCs, especially on the tolerogenic DC subset [151]. Their results indicated that the disturbance of the DCs-NK cells interaction and the tolerance function of DCs may contribute to the development of abnormal pregnancy outcomes during *T. gondii* infection. Vanders attributed the increased disease severity observed in pregnant women after influenza virus infection to the alterations in the number or function of DCs in pregnancy, which resulted in a significant reduced expression of key downstream antiviral factors, eg. IFN production. [152] Le Gars at al. found that pDCs exhibit an exaggerated pro-inflammatory immune response characterized by increased expression of MHC-II, CD69, IFN-γ-induced protein 10, and macrophage inflammatory protein 1β [25]. Inspiring by these initial studies, further studies should be carried on to explore the role of DCs in infection during pregnancy.

5. Therapeutic potential of dcs in pregnancy-associated diseases

The roles of DCs in pregnancy and pregnancy-associated diseases made it a promising target or tool of immunotherapy and vaccination. For example, as mature status or subgroup deviation of DCs play roles in RSA, any methods that obstruct the maturation of DCs or regulate DC differentiation have potential therapeutical effects. These regulators include chemical compounds, biological molecules, and other cells that interact with DCs. Rapamycin, heme oxygenase-1, and mesenchymal stem cells have been reported to decreased abortion rates in human or murine models [105,153,154]. Our previous study demonstrated that a traditional Chinese herb decoction Shou Tai Wan could treat RSA effectively by upregulating the percentage of pDCs and downregulating that of cDCs [155]. Baicalin may be one of the effective components in Shou Tai Wan (unpublished). Take into consideration that the ratio of cDC/pDC also abnormally increased in PE, whether the DC regulators listed above are protections for the PE patients need to be studied in the future.

In another aspect, syngeneic or manipulated DC themselves are feasible tools to cure RSA. Miranda, S., et al. found that adoptive transfer of syngeneic DCs alleviated the abortion in the mouse model, by upregulating the pregnancy-protective $CD8^+$ and T-cell receptor (TCR)-$\gamma\delta^+$ T cells, TGF-β1 and PG-induced blocking factor (PIBF) expression at

maternal-fetal interface [106]. DCs with modified Fas ligand (FasL) gene were used to provide a protective microenvironment in mouse model of spontaneous abortion [156]. The mechanism may be that FasL expressed on DCs cooperates with Fas expressed on activated decidual or peripheral T cells to induce the apoptosis of T cells; thereby, protecting the fetus from immuno-rejection [156]. However, therapies of DC transfusion and gene modification have not been applied to the clinic because of the insufficient data concerning the functions, safety, stability and specific migration paths of DCs *in vivo*.

Compared to their therapeutical effects, the more prospective application of DCs as vaccines for the pregnancy-associated diseases has not started yet. Inspirations on DC application in clinic come from the leading studies in preventing transplantation rejection and autoimmune diseases, as well as in the oncogenesis [157–160]. Despite of all the difficulties and limitations, DC-based therapies or vaccines still shows a good application prospect.

6. Future Directions

The mammalian pregnancy introduces a great challenge to the immune system. DCs, as discussed, are a key initiator and regulator of the immune response for maintaining maternal-fetal immunotolerance, homeostasis and meanwhile protecting the body from being infected by pathogenic microbes. The aberrant polarization and dysfunction of DCs would lead to various pregnancy-associated diseases. The key of DC- based immunotherapy relies on the transferred DCs could properly activate the immune effecter cells in the maternal-fetal interface, induce them to form an immunotolerance status, and overcome the possible subsequent inflammation responses. Nevertheless, there is still a long way to thoroughly understand the functions of DCs in pregnancy and explore efficient DC-based immunotherapy to pregnancy-associated diseases.

Declaration of Competing Interest

The authors report no declarations of interest.

Acknowledgements

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